REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been revised to include a section headed "Brief Description of the Drawings" as required by the Examiner. Introduction of the section does not raise the issue of new matter as the information contained therein comes directly from the Figures or, in the case of Figure 10, from page 9, lines 1 and 2.

The Examiner's renumbering of the claims is noted. Prior claim 18 has been cancelled without prejudice, thereby rendering moot the rejection thereof.

Claims 19 has been revised to include the limitation of now cancelled claim 24 (with the revision of claim 19, claim 23 has also been cancelled). Claims 20-29 have been revised to correct dependency necessitated by renumbering of the claims and/or claim cancellations. Claim 25 has been additionally revised for purposes of clarity.

Claim 30 has been revised to include the limitation of now cancelled claim 35 (with the revision of claim 30, claim 34 has also been cancelled). Claims 31-36 have been revised to correct dependency necessitated by renumbering of the claims and/or claim cancellations. Claim 36 has been additionally revised for purposes of clarity.

Claims 38-40, 42, 44 and 45 have been revised to correct dependency necessitated by the renumbering of the claims.

Claims 18-46 stand rejected under 35 USC 103 as allegedly being obvious over Martin et al. Cancellation of claim 18 moots the rejection thereof. Withdrawal of the rejection of claims 19-46 is submitted to be in order for the reasons that follow.

At the outset, the Examiner's attention is directed to the fact that claims 19 and 30 have been revised so as to indicate that the 2' carboxylic acid esters of Erythromycin B are with a dicarboxylic acid. The claims as now presented are unarguably novel over Martin et al.

Insofar as the rejection is based on obviousness, Applicants submit herewith, in the form of a Declaration by Dr. Barber, data that demonstrate the enhanced stability of a 2' carboxylic acid ester of Erythromycin B of the instant invention (that is, wherein the 2' ester is with a dicarboxylic acid) relative to a 2' ester of Erythromycin A (also dicarboxylic). Much of the data set forth in the attached Declaration was presented in the prior Amendment and is acknowledged by the Examiner in the October 16, 2003 Action as having been considered.

As will be clear from the Declaration, tests were conducted to establish the acid stability of Erythromycin B 2'-ethyl succinate (EBES), and Erythromycin A 2'-ethyl succinate (EAES) over a range of pH conditions likely to be encountered in the stomach of a human patient.

The results of the studies are set forth in Table 1 of the Declaration (paragraph 7), where half – lives, in minutes, of EBES and EAES at various pH values tested are presented. The results demonstrate the enhanced stability of EBES as compared to EAES

over a range of acid pH conditions. As stated in paragraph 8 of the Declaration, EBES was stable for about 70 mins at pH 2, greater than 180 mins at pH 2.5, and greater than 420 mins at pH 3. These values are to be compared with less than 5 mins at pH 2 and pH 2.5 and less than 10 mins at pH 3 for EAES.

The Declaration also describes results of a comparative degradation study under conditions mimicking a pediatric formulation. The data set forth in Table 2 of the Declaration (paragraph 9) clearly demonstrate the storage stability of the 2'-ester of Erythromycin B enol ester of the invention.

In summary, the data presented in the Declaration demonstrate enhanced stability of the Erythromycin B dicarboxylic acid ester tested as compared to the corresponding ester of Erythromycin A. Given the demonstrated stability of the Erythromycin B ester at pH values found in the stomach, on administration to a patient, the ester would pass to the intestine for absorption and conversion to Erythromycin B (by base-catalysed cleavage of the ester group) to generate free Erythromycin B as the active antibiotic. The 2' dicarboxylic acid esters of Erythromycin B are thus therapeutically useful antibiotics since they do not generate substantial amounts of degradation products, as do esters of Erythromycin A. When formulated as an orally administrable suspension (particularly for pediatric administration), there is some degradation of the 2' ester (dicarboxylic acid) to Erythromycin B during storage. Thus, there is some loss of the "taste masking" effect of the ester during storage. This disadvantage is overcome by the 2' carboxylic esters of Erythromycin B enol ether, also as demonstrated in the attached Declaration.

As pointed our previously, Martin et al discloses, in Table (III), the antibacterial activity of Erythromycin B (compound B) and its 2'-acetyl ester (compound 2B). Table (VII) discloses *in vitro* data for Erythromycin B but not the 2'-acetyl ester. With regard to the 2'-acetyl ester, the data shown in Table (III) are, as indicated, *in vitro* data and demonstrate that the ester is less active than the parent Erythromycin B. From a comparison of the "Log potency" values for compounds B and 2B as listed in Table (III), it will be apparent that compound 2B (the ester) is considerably less active than Erythromycin B itself.

Nothing in Martin et al would have suggested the stability under acid conditions (as encountered in the stomach) of Erythromycin B. For this reason, there would have been no suggestion of the advantages that are obtained by use of the 2' dicarboxylic acid esters of Erythromycin B of the instant claims (see again the attached Declaration). Thus, their use as a therapeutic agent would not have been rendered obvious by the citation (particularly since, as noted above, the *in vitro* data show the ester used to be less active than Erythromycin B).

Furthermore, the particular subject matter of claims 43-46 (relating to use of Erythromycin B *per se*) would not have been rendered obvious because the subject matter of these claims relies on an appreciation of the stability under acidic conditions of Erythromycin B and Martin et al would not have suggested such stability. The fact that Erythromycin B remains intact in the stomach means that it can be used for the treatment of "stomach resident" bacteria, an important example of which is *Helicobacter pylori*

(see claim 46). Nothing in the citation would have suggested the esters of the Erythromycin B enol ether. Indeed, the Examiner does not contend otherwise.

In view of the above, reconsideration is requested.

Claims 18-46 stand rejected under 35 USC 103 as allegedly being obvious over Booth or Blasina et al in view of Mordi et al. Withdrawal of the rejection is submitted to be in order in view of the Barber/Mordi Declaration submitted herewith that makes it clear that the J. Med. Chem. 2000 article upon which the Examiner relies (which published less than 1 year prior to the filing date of the PCT application from which this case derives) is not the publication of "another". Accordingly, the article is not prior art and the rejection must fail.

Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Mary J. Wilson

Mary J. Wilson
Reg. No. 32,955

MJW:tat
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100